Claims 2 and 3 are cancelled; claims 8-11 and 13 are amended; and claims 31-34 are added; as a result, claims 1, 4, 8-20 and 31-34 are now pending in this application. No new matter is added by the amendments to the claims or by the new claims.

Support for claim 31 (anti-tumor) can be found in originally filed claim 2, and in Examples 2 and 3. Support for claim 32 (anti-metastatic) can be found in originally filed claim 3, as well as in Example 2. Support for claim 33 (cytotoxic) can be found in Example 5. Support for claim 34 (anti-melanoma) can be found in originally filed claims 4 and 15, as well as in Example 1.

The amendments to the claims are made to add dependencies, and do not narrow the claims. Therefore, the amendments to the claims are not intended to surrender any range of equivalents to which the claims may be entitled, such as equivalents of any claim element which are not within the prior art.

I. The Rejection under 35 U.S.C. §103(a).

The Examiner rejected claims 1-4 and 8-20 under 35 U.S.C. §103(a) as obvious in light of Brandes (U.S. Patent No. 5,859,065). This rejection is respectfully traversed.

A *prima facie* case of obviousness has not been established. In order to establish a *prima facie* case of obviousness, three factors must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success at the time the invention was made. Third, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. See M.P.E.P. § 2143; In re Lee, 277 F.3d 1338, 61 U.S.P.Q.2d 1430 (Fed. Cir. 2002). It is respectfully asserted that the Examiner has not met these requirements.

Brandes teaches a method for treating cancer cells by first administering an intracellular histamine binding antagonist and then administering a traditional chemotherapeutic agent. Brandes discloses many intracellular histamine binding antagonists, including N, N-diethyl-2-[4-(phenylmethyl)-phenoxy]ethanamine (DPPE), as well as antidepressants, such as fluoxetine.

However, Brandes does not mention the terms serotonin, serotonin agent, serotonin reuptake inhibitor, or selective serotonin reuptake inhibitor. Additionally, Brandes discourages the use of compounds other than DPPE and its analogs (see col. 6, lines 16-25). In fact, Brandes teaches that the antidepressant group of drugs may cause cardiac conditions (see col. 6, lines 28-30).

Brandes teaches that the intracellular histamine binding antagonists promote malignant cell proliferation (see abstract; col. 4, line 37; col. 5, lines 43-45; Ex. X;) and that fluoxetine increases the proliferation of tumor cells (see col. 13, lines 23-30; Fig. 9B). Thus, there is no suggestion in Brandes that any serotonin agent would inhibit cancer or tumor growth. Moreover, there is no reasonable expectation that an anti-cancer, anti-tumor, anti-metastatic or cytotoxic effect would be achieved by administering a serotonin agent, since Brandes teaches that antidepressants (including fluoxetine) would increase the proliferation of tumor cells.

Applicants have discovered that serotonin agents have the opposite effect of that reported in Brandes. The instant claims are directed to therapeutic methods that comprise the administration of an anti-cancer, anti-tumor, anti-metastatic or cytotoxic amount of a serotonin agent. It is respectfully submitted that Brandes does not teach or suggest the claimed methods and that Brandes would not have provided any reasonable expectation that serotonin agents would have the recited anti-cancer, anti-tumor, anti-metastatic or cytotoxic effect. Therefore, it is respectfully submitted that claims 1-4 and 8-20 are not obvious in light of Brandes, and withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

II. The Rejections under 35 U.S.C. §112 (first paragraph).

The Examiner rejected claims 1, 2, 8-14 and 16-18 under 35 U.S.C. §112 (first paragraph), asserting that the specification is not enabling for the term "cancer" or "tumor growth." Specifically, the Examiner asserts that the terms "cancer" and "tumor growth" lack clear exemplary support in the specification. The Examiner also asserts that the art of cancer therapy is highly unpredictable and that there are no examples of compounds that are efficacious against cancer, in general. The Examiner concluded that one of skill in the art could not use the entire scope of the invention without undue experimentation, due to the unpredictable nature of

the invention, the lack of guidance and working examples, and the broad claims. This rejection is respectfully traversed.

The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? M.P.E.P. 2164.01. Relevant factors that can be considered to determine whether this standard has been met were outlined by the Court of Appeals for the Federal Circuit in In re Wands, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). These factors include: (1) the quantity of experimentation necessary (time and expense); (2) the amount of direction or guidance presented; (3) the presence or absence of working examples relating to the invention; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. The determination that undue experimentation would have been needed to practice the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all factual considerations, including the eight factors identified above. In re Wands (8 U.S.P.Q.2d at 1404 (Fed. Cir. 1988)).

An analysis of the factors from In re Wands (8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988)) shows that it would not require undue experimentation to practice the present invention as claimed. (1) *The quantity of experimentation necessary.* When analyzing whether it requires "undue experimentation" to practice claimed methods, the key word is "undue" not "experimentation." In re Angstadt, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). Enablement is not precluded by the necessity for some experimentation, such as routine screening. In fact, a considerable amount of experimentation is permissible if it is merely routine, or the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should take. Ex parte Jackson, 217 U.S.P.Q. 804, 807 (Bd. App. 1982). The specification provides 5 working examples and 2 prophetic examples, which studied a specific type of cancer, melanoma. A person of skill in the art would be able to screen other cancer types by simply replacing the type of cancer found in the example with the type of cancer of interest. It is respectfully submitted that the fact that different types of cancer would have to be screened to

confirm that they are amenable to the treatment as claimed by Applicants would not constitute "undue experimentation," particularly in an art where the level of skill is high. In re Wands, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988).

(2) *The amount of direction or guidance presented.* Applicants' specification provides sufficient guidance to allow one of skill in the art to practice the claimed invention. For example, there is a discussion of cancer, malignant neoplasms, and chemotherapy on page 1, lines 22-29. A particular type of neoplasm, melanoma, is discussed on page 2, line 29 through page 3, line 3. The "inhibition of tumor cell growth" is defined at page 6, lines 7-10. A model for studying the inhibition of tumor growth is found in Example 2. Example 3 provides a model for determining if tumor growth could be inhibited and if body fat loss could be prevented using the method of Applicants' claims.

(3) *The presence or absence of working examples relating to the invention.* The specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation. M.P.E.P. § 2164.02. Additionally, an *in vitro* or an *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. M.P.E.P. § 2164.02. Examples 1-3 and 5 in the specification disclose *in vitro* and *in vivo* models and screening procedures which can be used to demonstrate the ability of a serotonin agent to inhibit tumor cell growth, and to have a cytotoxic effect on cancer cells. In Figures 6 and 7, data are presented which show that fluoxetine administration decreases the rate of tumor growth in mice.

Thus, Applicants respectfully submit that the instant specification contains *in vitro* and *in vivo* models which constitute working examples that clearly support the recited utility and enable the practice of the claimed method.

(4) *The nature of the invention.* The nature of the invention is a method to treat cancer. Cancer has been known for many years, has been well researched and a variety of methods to treat cancer are available. Additionally, there are numerous *in vitro* and *in vivo* models that are routinely carried out that can be used to identify agents with useful anti-cancer properties. Furthermore, the U.S. Patent & Trademark Office has recognized the patentability of methods to

treat cancer by administration of a compound, see for example U.S. Patent No. 5,981,541 (specifically claim 24), U.S. Patent No. 6,040,342 (specifically claim 11), and U.S. Patent No. 6,030,961 (specifically claim 17), a copy of each is enclosed herewith for the Examiner's convenience. Thus, the instant invention falls within a well established field.

(5) *The state of the prior art.* Cancer therapy is not a new field. For years, therapies for treating cancer have been available. Currently, there are a number of drugs on the market for treating cancer and for inhibiting tumor growth. For example, there are topoisomerase I inhibitors known in the art to be useful for treating cancer, such as camptothecin and its structurally-related analogs (see page 1, line 27 through page 2, line 8 of the instant specification). Furthermore, as evidenced by the above listed patents, methodologies for treating cancer are also well known to the art. Therefore, Applicants respectfully submit that the state of the prior art is well developed. As a result, one skilled in the art would have access to a body of assays and techniques that could be useful for evaluation of Applicants' claimed methods to effectively treat cancer and inhibit the growth of tumors.

(6) *The relative skill of those in the art.* The relative skill of those in the art is high. Generally, one considered of skill in the art for the instant invention will have an advanced degree, either an M.D., a Ph.D. or both.

(7) *The predictability or unpredictability of the art.* The fact that the outcome of a screening program is unpredictable is precisely why a screening program is carried out. For example, the Federal Court has explicitly recognized that the need, and methodologies required, to carry out extensive screening programs to locate bioactive molecules do not constitute undue experimentation. In In re Wands, 8 U.S.P.Q.2d 1400, 1406-1407 (Fed. Cir. 1988), the court stated:

> The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody.

Likewise, practitioners of the art related to the present application would be well-equipped to screen a given serotonin agent to confirm its ability to treat a selected form of cancer, with the

methods claimed by Applicants. See also, Hybritech Inc. v. Monoclonal Antibodies Inc., 231 U.S.P.Q. 81, 84 (Fed. Cir. 1986) (evidence that screening methods used to identify characteristics [of monoclonal antibodies] were available to art convincing of enablement). Thus, the fact that one of skill in the art would need to screen a serotonin agent to confirm its ability to treat a selected form of cancer does not constitute "undue experimentation," particularly in an art area in which the level of skill is very high and in which the screening of large numbers of compounds has been standard practice for years. (Ex parte Forman, 230 U.S.P.Q. 546 (Bd. App. 1986)).

(8) *The breadth of the claims*. Claim breadth alone does not provide the basis for a nonenablement rejection. In re Moore, 169 U.S.P.Q. 236 (C.C.P.A. 1971). The scope of enablement provided by Applicants need only bear a "reasonable correlation" to the scope of the claims. In re Fisher, 166 U.S.P.Q. 18, 24 (C.C.P.A. 1970). Applicants have adequately described how to use their methods to treat cancer and inhibit tumor growth. Furthermore, Applicants respectfully submit that the claims are not overly broad. Practitioners in this are highly knowledgeable of the many types and forms of cancer. Thus, Applicants respectfully submit that the scope of enablement provided by Applicants' specification is sufficient for the breadth of the instant claims.

The first paragraph of 35 U.S.C. § 112 requires no more than a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of the claims. The above analysis of the factual considerations outlined by the court in In re Wands and applied to the present application demonstrate that the claimed invention can be practiced without undue or unreasonable experimentation. Thus, Applicants respectfully submit that the instant application complies with 35 U.S.C. § 112, first paragraph.

Furthermore, the Examiner has not provided any factual evidence to suggest that the instant specification fails to provide adequate guidance to enable one skilled in the art to practice the claimed invention. Thus the Examiner has failed to meet the burden required to establish a rejection of the instant claims under §112. Claim 1 recites a straightforward method to treat cancer, comprising administering to a mammal in need an effective amount of a serotonin agent. Claim 14 recites a straightforward method, comprising contacting cancer cells with an effective amount of a serotonin agent. The specification provides examples of how the method can be

practiced *in vitro* and *in vivo*. Therefore, it is respectfully submitted that the instant specification provides adequate guidance to enable one skilled in the art to practice the claimed invention.

Additionally, it is not the function of the claims to exclude all possibly inoperable embodiments. In re Anderson, 471 F.2d 1237, 176 U.S.P.Q. 331 (C.C.P.A. 1973); Atlas Powder Co. v. E.I. Du Pont De Nemours & Co., 224 U.S.P.Q. 409 (Fed. Cir. 1984); In re Dinh-Nguyen, 181 U.S.P.Q. 46 (C.C.P.A. 1974). Rather, it is the specification that must be evaluated to determine whether or not the specification would enable the art worker to practice the invention without undue experimentation. Ex parte Forman, 230 U.S.P.Q. 546 (B.P.A.I. 1986). As discussed above, the specification provides adequate guidance to allow one of skill in the art to determine whether a particular cancer is susceptible to treatment using a claimed method without undue or unreasonable experimentation. Therefore, Applicants' specification is enabling and meets the requirements of 35 U.S.C. §112 (1). Accordingly, withdrawal of the rejection under 35 U.S.C. § 112 (first paragraph) is respectfully requested.

The Examiner also rejected claims 1-4, 8-10, 13-16 and 19-20 under 35 U.S.C. §112 (first paragraph), asserting that the specification was not enabling for the terms "serotonin agent" or "serotonin uptake inhibitor." Specifically, the Examiner asserted that the specification does not enable any person skilled in the art to which it pertains to use the invention commensurate in scope with Applicants' claims. The Examiner also asserted that the terms "serotonin agent" and "serotonin reuptake inhibitor" lack clear exemplary support in the specification. This rejection is respectfully traversed.

The test of enablement is whether one skilled in the art could make or use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation. M.P.E.P. § 2164.01. The Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. In re Wright, 999 F.2d 1557, 27 U.S.P.Q. 2d 1510 (Fed. Cir. 1993). In the present rejection, the Examiner has not provided any analysis to support this rejection and thus, the Examiner has not provided a reasonable basis to question the enablement of the claimed invention. Therefore, the Examiner is respectfully requested to withdraw this rejection.

It is respectfully submitted that Applicants' specification provides sufficient guidance to allow one of skill in the art to practice the claimed invention. The Examiner is referred to the thorough Wands analysis on the enablement of the pending claims as provided above. Under M.P.E.P.§ 2164.02, a specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation. However, the specification provides *in vitro* and *in vivo* models and screening procedures which can be used to determine the effect of a serotonin agent on cancer cell growth and tumor growth. Thus, Applicants submit that the instant specification provides working examples that clearly support the recited utility and enablement of the claimed method.

Furthermore, the terms "serotonin agent," "serotonin reuptake inhibitor," and "selective serotonin reuptake inhibitor" are well recognized in the art and are adequately defined and discussed on page 5, line 23 through page 6, line 6. Thus, one of skill in the art could properly look to the state of the art of cancer treatment for useful guidance with respect to screening and determining which serotonin agents would be effective to treat cancer. Therefore, Applicants respectfully submit that ample disclosure has been provided, with respect to a method of treating cancer or inhibiting tumor growth with an effective amount of a serotonin agent, as claimed by Applicants, to enable the art worker to practice the invention as claimed. Thus, Applicants' specification is enabling and meets the requirements of 35 U.S.C. §112 (1). Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112 (first paragraph).

In the event this rejection is maintained, Applicants respectfully request the Examiner to provide evidence and a reasoned analysis to support the rejection, in a subsequent non-final office action so that Applicants can fully address the Examiner's grounds for the rejection.

Conclusion

It is respectfully submitted that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicants' attorney (612-349-9580) to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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CERTIFICATE UNDER 37 C.F.R. 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner of Patents, Washington, D.C. 20231, on this 25 day of June, 2002.

Jane E. Brockschink
Name

_____
Signature